Empyema occurs in nearly 1 in 150 children hospitalised with pneumonia, affecting about 3.3 per 100,000 children. The management of childhood empyema poses a therapeutic challenge as management decisions in children cannot be made by extrapolating data from adult studies. The major difference between adult and childhood empyema is that pneumonia progressing to empyema usually occurs in a previously well child, so the clinical outcome is usually excellent despite significant morbidity. Conversely in adults, empyema causes significant mortality of up to 20%. Therapeutic options currently available include: systemic antibiotics alone or in combination with thoracocentesis; chest drain insertion, with or without instillation of fibrinolytic agents; and surgical techniques such as video-assisted thoracoscopic surgery, mini-thoracotomy, and standard thoracotomy with decortication (removal of the fibrinous ‘peel’ from the lungs). There have been many recent publications reviewing the evidence available for the treatment of empyema in children, including the British Thoracic Society guidelines on the management of pleural infection in children (www.brit-thoracic.org.uk), a state of the art in the management of empyema in children and a meta-analysis comparing primary operative with non-operative therapies for paediatric empyema. As this review concentrates on discuss-
ing the evidence in the context of measurable outcome measures, mainly from prospective studies where available and some relevant retrospective studies, readers are encouraged to refer to these articles in addition.

**POTENTIAL PROGNOSTIC FACTORS AND OUTCOME MEASURES**

Prognostic factors that may determine the course of the disease include: initial white cell counts; C-reactive protein levels; the radiological appearance, including ultrasonographic changes, which are useful in staging the disease; identification of the causative organism; and pleural fluid biochemistry including lactate dehydrogenase, pH, glucose and protein.\(^5\) However, although factors such as the biochemical composition of the pleural fluid are used to guide management in adults, there are no good data available in children to support their use. In addition, as the acquisition of pleural fluid is invasive, this is generally avoided in paediatrics, in stark contrast to the practice in adult patients.

The aim of treatment of empyema is to sterilise the pleural fluid and allow a restitution of normal lung function. As discussed above, adult outcome measures such as mortality cannot be extrapolated to the paediatric population. Hence, studies in paediatric patients utilise surrogate end-point markers to compare treatment modalities (Table 1).

Ultimately, it is the clinical well-being of the patient, functional outcome measures and cost analysis that play a role in the selection of one therapeutic approach over another. However, as many of the studies include children less than 5 years of age, lung function data are not available in these series. The current best available data utilise length of stay as the primary outcome measure.

**TREATMENT OPTIONS**

**Antibiotics alone**

Several studies have suggested that chest tube drainage may not be necessary in children if appropriate antibiotic therapy and supportive care are provided, particularly in those with smaller (less than 10 mm thickness) pleural collections.\(^6\)\(^7\) Data from these studies indicate that patients who present with smaller pleural collections will have a similar length of hospital stay if treated by either antibiotics alone or operative interventions. However, these studies were retrospective and had considerable heterogeneity of the study population.

Antibiotics alone have a role in small effusions with which the child has no respiratory compromise. The choice of antibiotic is largely dependent on local guidelines, reflects whether the infection was community or hospital acquired and depends on the child’s underlying immune status. A broad-spectrum antibiotic to ensure the adequate treatment of *Streptococcus pneumoniae* and a consideration of anti-staphylococcal cover, particularly in the presence of pneumatoceles, is recommended. If the child fails to respond after 48 hours and there is respiratory compromise or evidence of an enlarging effusion on either chest X-ray or ultrasound, drainage of the effusion is advocated.\(^5\)

**Thoracocentesis**

A retrospective review of 67 children treated by thoracocentesis or catheter drainage of parapneumonic effusions had similar complication rates and lengths of stay, but children who underwent thoracocentesis had significantly higher reintervention rates.\(^8\) Shoseyov et al.\(^9\) compared repeated thoracocentesis and chest tube drainage in 67 children in a prospective study. Thirty-five children received repeated ultrasound-guided needle thoracocentesis on alternate days on a mean of 2.4 occasions under local anaesthetic.\(^9\) Five children failed to respond (two had tube drainage plus urokinase, and three had surgery). There was no difference between the groups in duration of pyrexia or
of hospital stay. The authors concluded that treatment with repeated thoracocentesis is as effective as chest drainage. However, the study was not randomised and the two treatments were carried out in separate hospitals. It is our view that if a child requires an intervention, early chest drain insertion is recommended in order to minimise repeated trauma to the child.

**Chest drain insertion alone**

There are three prospective studies looking at chest tube drainage, which are summarised in Table 2. The hospital stay in these studies varied between 14 and 24 days, and all patients made a complete recovery. However, the prolonged length of hospital stay, when compared with other intervention studies discussed below, has significant health economic implications. A similar median hospital stay (14.5 days) was observed in a retrospective study of clinical practice at Great Ormond Street Hospital for Children.10 During this period, 54 patients were treated: 7 patients were treated successfully with antibiotics alone, whereas 47 patients required chest drain insertion, and of these 21 required further surgical intervention. It is likely that the discrepancy between the two studies with regard to need for further surgical intervention is due to patient referral demographics, as Great Ormond Street Hospital is a tertiary referral centre receiving patients referred from other hospitals, and the patients are thus more likely to have had the illness for a longer period.

**Chest drain with intrapleural saline**

The two prospective studies that looked at this treatment option mainly used it in the placebo group (Table 3). Nevertheless, the reported hospital stay of 9.5 days is less than that with chest tube drainage alone.

**Chest drain with intrapleural fibrinolytics**

Fibrinolytics are instilled into the pleural cavity to lyse fibrinous strands and clear lymphatic pores, thus facilitating better drainage. There have been a number of published reports on the use of fibrinolytics in children, but only four are randomised controlled trials (Table 4).13–16 The case series reports describe the management in more than 300 children using streptokinase, urokinase, alteplase or tissue plasminogen activator using different protocols, and mainly in children who fail to respond to chest tube drainage alone. It is evident that the use of fibrinolytics is safe as the success rate in these series was approximately 80–90%, with the major side effect being pain during administration.

Two randomised prospective studies of intrapleural urokinase are from the UK. The first one was a multicentre study of 60 patients undertaken on behalf of the British

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**Table 2** Outcome measures of chest drain insertion alone

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Hospital stay (mean number of days)</th>
<th>Chest drain (mean number of days)</th>
<th>Number of treatment failures</th>
<th>Cost</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoseyov et al. 9</td>
<td>2002</td>
<td>32</td>
<td>24</td>
<td>NS</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>Satish et al. 11</td>
<td>2003</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>0</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>Karaman et al. 12</td>
<td>2004</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>NS</td>
<td>NS</td>
<td>0</td>
</tr>
</tbody>
</table>

NS: not specified.

**Table 3** Outcome measures of chest drain with intrapleural saline

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Hospital stay (mean number of days)</th>
<th>Chest drain (mean number of days)</th>
<th>Number of treatment failures</th>
<th>Cost</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson et al. 13</td>
<td>2002</td>
<td>29</td>
<td>9.5</td>
<td>NS</td>
<td>3</td>
<td>NS</td>
<td>0</td>
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<tr>
<td>Singh et al. 14</td>
<td>2004</td>
<td>21</td>
<td>NS</td>
<td>NS</td>
<td>5</td>
<td>NS</td>
<td>0</td>
</tr>
</tbody>
</table>

NS: not specified.

**Table 4** Outcome measures of chest drain with intrapleural fibrinolytics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Hospital stay</th>
<th>Chest drain</th>
<th>Number of treatment failures</th>
<th>Cost</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson et al. 13*</td>
<td>2002</td>
<td>29</td>
<td>7.4</td>
<td>NS</td>
<td>2</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>Singh et al. 14#</td>
<td>2004</td>
<td>19</td>
<td>NS</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>Sonnappa et al. 15*</td>
<td>2006</td>
<td>30</td>
<td>6</td>
<td>NS</td>
<td>5</td>
<td>$9,127</td>
<td>0</td>
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<tr>
<td>Kurt et al. 16†</td>
<td>2006</td>
<td>7</td>
<td>13</td>
<td>9.6</td>
<td>0</td>
<td>$21,947</td>
<td>0</td>
</tr>
</tbody>
</table>

*Urokinase, #streptokinase, †reteplase; NS: not specified.
Paediatric Respiratory Society Empyema Study Group. Patients were randomised to receive either 40,000 units of urokinase in 40 ml saline (10,000 units in 10 ml saline if under 1 year) or 0.9% saline instilled twice a day over 3 days. The urokinase group demonstrated a significant reduction in length of hospital stay compared with the saline control group (7.4 versus 9.5 days). Five patients (two in the treatment arm) failed treatment and required surgical decortication.

In the only other prospective randomised controlled study of intrapleural urokinase conducted at Great Ormond Street Hospital, we compared intrapleural urokinase with video-assisted thoracoscopic surgery (VATS) in 60 children. Patients were randomised to receive either percutaneous chest drain with intrapleural urokinase or VATS. The VATS group had a median post-intervention hospital stay of 6 days (range 3–16 days) compared with a mean hospital stay in the urokinase group of 6 days (range 4–25 days). This is the only study to demonstrate no significant difference in duration of hospital stay between intrapleural urokinase and primary VATS for the treatment of empyema in children.

The failure rates were similar in both treatment arms: five patients in the urokinase arm did not respond to conservative management and had to proceed to having secondary VATS with or without mini-thoracotomy, and four patients in the VATS arm had the operation converted to a mini-thoracotomy. In addition, we reviewed chest-X rays at 6 months and, although the majority were abnormal with slight thickening of the pleura, there were no differences between the two groups.

Cost analysis showed that the mean treatment cost of patients in the urokinase arm was lower than that in the VATS arm ($9127 versus $11,379). Thus, the costs in the VATS arm exceeded those in the urokinase arm by 25%. We concluded, on a cost basis, that intrapleural urokinase is the better choice as the therapies were equivalent in every other measure.

Another prospectively controlled study of fibrinolytics from India randomised 40 children to receive either intrapleural streptokinase or normal saline. No difference was noted in all outcome measures between the groups. In the only other study of fibrinolytics, 18 children were randomised to receive either chest drain or VATS. Seven children received intrapleural reteplase and had a mean hospital stay of 13 days, compared with the VATS group who had a hospital stay of 6 days. There were no treatment failures in either group, and there was no significant difference in costs between the groups. The drawback of this study was that intrapleural reteplase was used as salvage therapy rather than primary therapy.

**Surgery**

The surgical options are mini-thoracotomy, open decortication and VATS. A mini-thoracotomy is an open debridement procedure performed through a small incision. Open decortication involves removal of the thickened pleural rind and irrigation of the pleural cavity through a large posterolateral scar. VATS is thoracoscopic decortication performed through two or three ports made in the chest.

**Open decortication**

In a review of 18 patients who underwent primary open decortication, the median hospital stay was 4 days and the authors concluded, somewhat controversially, that fibrinolytics and VATS had no place in stage III empyema. A retrospective review of treatment in 48 children found a hospital stay of 15 days for chest drains, 8 days for fibrinolytics and 6.5 days for thoracotomy. The only prospective study to compare open thoracotomy and chest tube drainage showed a shorter hospital stay in the thoracotomy group (9.5 days versus 15.4 days). (Table 5). The limitations of this study have previously been discussed.

**VATS**

VATS has been shown to be safe and effective in children for various conditions. VATS was initially used as salvage therapy following the failure of medical treatment for empyema. However, the use of VATS to treat empyema in children has been increasing over the past decade, and it is being increasingly used as primary therapy.

A retrospective review of treatment options demonstrated that patients undergoing primary VATS had a significantly reduced number of procedures and a shorter hospital stay compared with those who had secondary VATS or open decortication for failed medical treatment. There are no studies that directly compare primary VATS with open decortication in children. Our study, discussed above, is the only prospective study comparing primary VATS and secondary VATS with open decortication.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Hospital stay (mean number of days)</th>
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<tr>
<td>Karaman et al. 12#</td>
<td>2004</td>
<td>15</td>
<td>9.5</td>
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<td>Sonnappa et al. 15*</td>
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<td>10</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>$19714</td>
<td>0</td>
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</tbody>
</table>

*Video-assisted thoracoscopic surgery; #Open decortication; NA: not applicable; NS: not specified.
fibrinolytics. As mentioned above, Kurt et al.\textsuperscript{16} compared VATS and chest tube drainage with salvage reteplase and found that all outcome measures were better in the VATS group than the chest drain group. The authors concluded that VATS is superior to chest drain insertion. It is interesting to note that the mean hospital stay in the VATS group in this study was 6 days, which is similar to that of the urokinase group in our study\textsuperscript{15} despite the VATS procedure being carried out in the early stages of the disease.

A meta-analysis comparing the results of non-operative and primary operative therapy for the treatment of paediatric empyema reviewed 67 studies.\textsuperscript{1} Data were aggregated from reports of children initially treated non-operatively (3418 cases from 54 studies) and from children treated with a primary operative approach (363 cases from 25 studies). Analysis of the data showed that primary operative therapy was associated with a lower mortality rate, lower reintervention rate, shorter length of hospitalisation, decreased time with a thoracostomy tube, and shorter course of antibiotic therapy, compared with non-operative therapy.

The limitations of this analysis are that most of the studies included were observational or retrospective case note reviews. The study’s observational data show that the length of stay was similar for primary fibrinolytic therapy compared with thoracotomy and VATS (10.7 versus 10.6 versus 11.2 days, respectively). The analysis also infers that current surgical options for childhood empyema seem safe, with no reported mortality and little morbidity, and that there is complete resolution of the disease whatever the treatment.

DISCUSSION

The limited prospective studies reviewed above demonstrate that all the treatment options currently available are effective and safe in the treatment of childhood empyema. The controversy surrounding optimal treatment is increased by the lack of uniformity in outcome variables and the heterogeneity of the study population. The most consistently reported outcome measure is hospital stay after intervention. Hospital stay in the studies using intra-pleural urokinase\textsuperscript{13,15} compare favourably with hospital stay following VATS.\textsuperscript{15,16}

Only two studies look at the cost implications of treatments. Our study showed that the VATS option was 25% more expensive than the urokinase option,\textsuperscript{15} whereas the American study did not show a significant difference.\textsuperscript{16} This difference could be due to the fact that hospital stay for both treatment options was similar in our study, whereas the hospital stay was longer in the American study as reteplase was used as salvage therapy. Other outcome measures such as pain associated with the intervention and long-term lung function have not been looked at in any of the studies.

As the disease process is dynamic, it has been suggested that a step-wise treatment approach may be beneficial depending on the staging of empyema. The study by Sonnappa et al.\textsuperscript{15} showed no difference between ultrasound stages, but the study was not sufficiently powered to detect a difference.

Outcome predictors such as radiological findings at presentation, biochemical markers and bacteriology, including serotypes, also need to be studied in detail in adequately powered prospective randomised controlled studies. Sonnappa et al.\textsuperscript{15} looked at radiological outcome at 6 months follow-up and found no difference between the VATS and urokinase groups, but functional studies are ultimately required.

A further area, which requires substantiating, is the role of small percutaneous chest drains. It is current surgical practice to insert large, stiff, bored drains to ‘facilitate maximal drainage’. These have the disadvantages of limiting movement, coughing and mobilising due to pain. In Thomson’s study, post hoc subgroup analysis revealed a shorter length of stay in those children who had received a smaller percutaneous drain.\textsuperscript{13} This observation was also seen in a retrospective review of treatment options.\textsuperscript{20} In the study by Sonnappa et al.\textsuperscript{15}, in which VATS was compared with urokinase, all children in the urokinase arm had a small (8–12 Fr), soft percutaneous drain inserted.

FUTURE WORK

Pneumococcal prevention

Pneumococcus is the primary cause of community-acquired pneumonia and empyema in the developed world. The UK has recently introduced routine childhood immunisation with the heptavalent pneumococcal conjugate vaccine, but this vaccine does not contain the antigen for serotype 1. Although the introduction of this vaccine in the USA in 2001 has significantly reduced invasive pneumococcal disease in children, an increase in the number of cases of empyema has been reported.\textsuperscript{21} The disease in the vaccinated children was exclusively caused by non-vaccine serotypes, serotype 1 being the most common. Furthermore, a recent review of 75 cases of empyema from the UK suggests that the severity of the underlying pneumonic process seems to be increasing with associated necrosis and cavitatory disease.\textsuperscript{22} Streptococcus pneumoniae was the most common causative pathogen identified, and a high proportion of these were serotype 1. However, the authors could not demonstrate the serotype associated with cavitatory disease due to insufficient numbers.

The UK data on serotype prevalence are supported by recent studies from other countries such as Spain,\textsuperscript{23} Belgium\textsuperscript{24} and France.\textsuperscript{25} For those with invasive pneumonia, the theoretical coverage of a heptavalent vaccine was 37.2% compared with 79% coverage for a nonavalent vaccine. These values are similar to that seen in a randomised trial of a nonavalent vaccine in South Africa and Gambia.\textsuperscript{26,27} A predominance of serotype 1 among cases of pneumococcal empyema has been reported in a number of studies.\textsuperscript{28–31}
The Health Protection Agency in the UK has introduced a long-term enhanced programme of pneumococcal surveillance for the identification of pneumococcal serotypes causing paediatric empyema in England and Wales. Other countries such as Australia and New Zealand are also currently involved in enhanced pneumococcal surveillance. This will allow long-term monitoring of the frequency and severity of this condition, and for the surveillance of changes in the patterns of serotype prevalence in relation to the introduction of new vaccines, the ultimate goal being to prevent pneumococcal disease in children.

Treatment

There is interest in developing more potent treatment modalities for patients with empyema. More specific fibrinolytic treatments such as single-chain urokinase plasminogen activator and recombinant human deoxyribonuclease in combination with fibrinolytics, which inhibit fibrinoid adhesions and thereby prevent intrapleural loculations, have recently been tried successfully on animal models, and clinical trials are awaited.

Future directions are thus:

- determination of the role of heptavalent versus nonavalent pneumococcal conjugate vaccines in reducing the incidence of childhood empyema;
- enhanced surveillance to monitor increases in the prevalence of non-vaccine serotypes;
- prospective randomised studies with appropriate outcome measures to compare available treatments;
- evaluation of the role of small, soft percutaneous drains in future comparisons;
- the development of more specific fibrinolytics for childhood empyema.

CONCLUSION

It is clear that, irrespective of the intervention a child receives, the clinical outcome is excellent. In order to refine our choices of treatment and our inherent biases, there is a need for prospective studies to be conducted to directly compare available treatment options with additional long-term outcome measures such lung function. In an era of health rationalisation, cost analysis becomes increasingly important and should be included in these studies.

REFERENCES


**CME SECTION**

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**Educational questions**

Answer true or false to the following questions:

1. With regard to childhood empyema
   a. The incidence is 1 in 15 children hospitalised with pneumonia affecting 3.3 per 100,000 children
   b. The incidence is decreasing after the introduction of childhood pneumococcal vaccine
   c. It is associated with significant morbidity and mortality
   d. The most common causative organism in the UK is Staphylococcus aureus
   e. Streptococcus pneumoniae serotype 1 is covered in the heptavalent conjugate vaccine

2. The following are useful in predicting prognosis in childhood empyema
   a. Initial white cell count
   b. C-reactive protein
   c. Pleural fluid pH
   d. Pleural fluid glucose
   e. Pleural fluid lactate dehydrogenase

3. Regarding various treatment options for childhood empyema
   a. Urokinase is preferred over other fibrinolytics such as alteplase and streptokinase
   b. Simple parapneumonic effusions may be successfully treated with repeated thoracentesis
   c. There is no benefit in using VATS over intrapleural urokinase in multiloculated empyemas
   d. Small-bore chest drains should be avoided as they are easily blocked by thick pus
   e. Recombinant human deoxyribonuclease has been used successfully in some centres

4. Imaging in childhood empyema
   a. Pleural ultrasound is useful in identifying loculations and staging disease
   b. All patients should have a CT chest scan before treatment
   c. Chest X-ray is useful for monitoring the resolution of empyema
   d. Ventilation/perfusion scans are recommended to assess function
   e. It may take more than 4 weeks for the chest X-ray to return to normal after successful treatment

5. With regards to outcome in childhood empyema
   a. Nearly all children make a full recovery irrespective of the treatment received
   b. Mortality is similar to that in adults
   c. Chest X-ray is normal at 6 months follow-up
   d. Lung function (spirometry) is normal at 3 months after treatment
   e. Hospital stay is shorter in patients treated with VATS than with open decortication